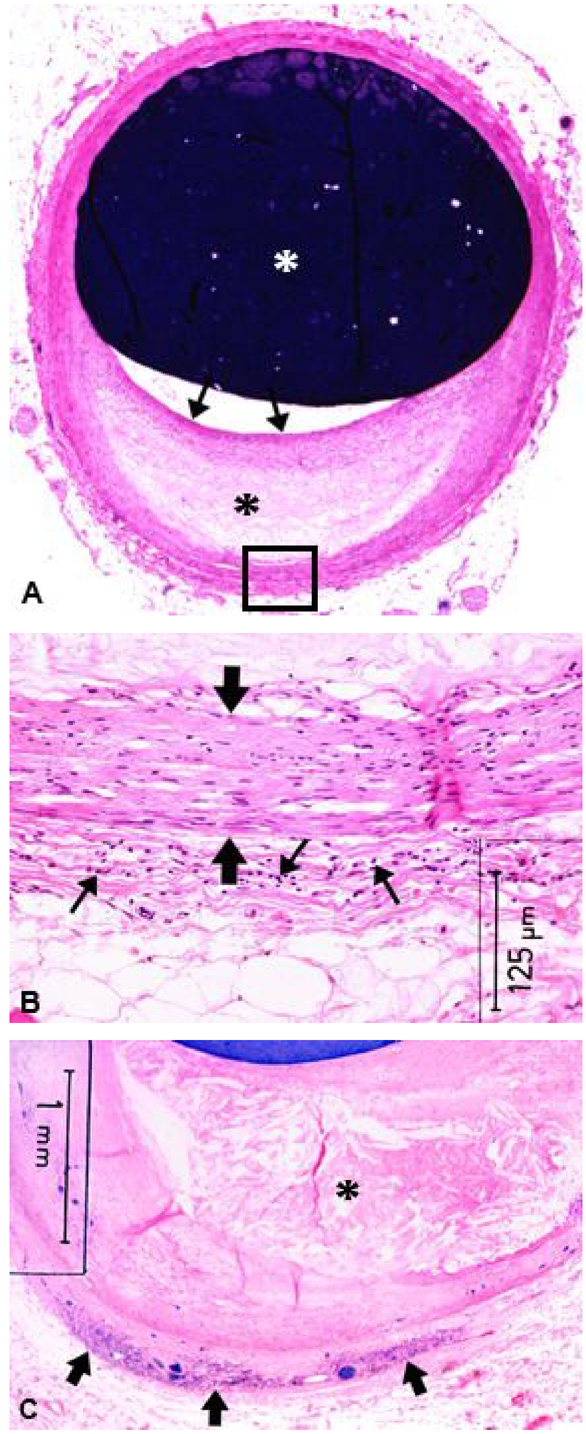
3. Inflammation. A Sign of Active Disease

"The lesions of atherosclerosis represent a series of highly specific cellular and molecular responses that can best be described, in aggregate, as an inflammatory disease."
Russell Ross, [18]



Chronic Inflammation

Atherosclerosis is a chronic inflammatory disease characterized by migration of monocytes and T lymphocytes to the area of arterial wall injury [1,18,45]. Early investigators also noted that the lipid-rich atherosclerotic plaque may develop secondary to a primary inflammatory process [46]. Inflammation per se, acute or chronic, is believed to be primarily defensive or protective in nature, its principal aims being to neutralize and remove the IA, and to initiate the process of tissue repair and healing [18,47]. However, the inflammatory mediators associated with inflammatory cells are also potentially harmful because they can damage tissue and aggravate injury. The presence of T lymphocytes with an atherosclerotic plaque indicates that the immune system has been activated, that the IA, or a product thereof, is a foreign agent or antigen, and that antibodies are being produced against it [48–50]. We can surmise, based on the migration of monocytes and T lymphocytes to the area of injury, that the IA initiating the development of atherosclerosis represents a significant threat to the organism, and that all appropriate defenses are being mobilized against it. It should be emphasized that inflammatory cell infiltrates are found only within or overlying atherosclerotic plaques. They are not found in relation to a normal intima that has no evidence of atherosclerosis [51,52], (Figure 5, Figures 5A,5B). The migration and infiltration of chronic inflammatory cells, i.e., monocytes and T cells, reflect "active" inflammatory atherosclerotic disease [18,48,53].

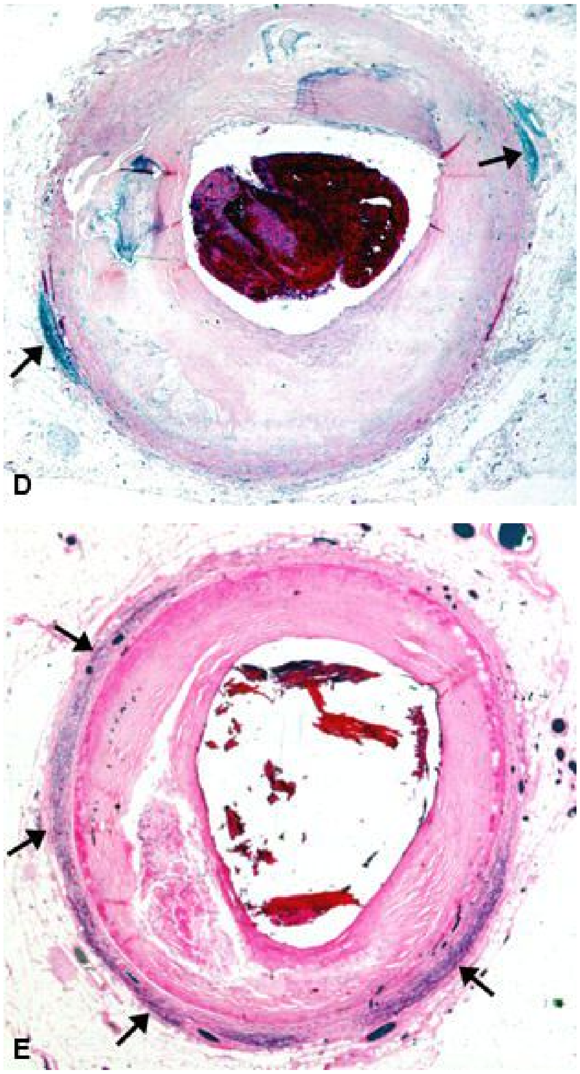


Figure 5: **A**, Proximal RCA section from a 32-year-old Asian male showing a small asymmetric plaque, with a necrotic core (black asterisk) and a fibrous cap (black arrows). White asterisk = lumen. H & E stain. Magnification x19.5. **B**, High-power view of rectangle in **A**, of the adventitia showing scattered Tcells (thin arrows). This amount of inflammatory response was classified as Grade I. Media = fat arrows. H & E stain. **C**, Large asymmetric atheroma (asterisk) in a 51-year-old white female with Grade II inflammation of the adventitia (arrows). Lumen at top of photo. H & E stain. **D**, Mid-RCA section from a 72-year-old white male. The luminal stenosis is estimated to be 80% and the lumen contains a thrombus. Two foci of T cells can be seen in the adventitia (arrows) on opposite sides of the lumen. This is classified as a Grade III inflammatory response. H & E stain. Magnification x11.2. **E**, Distal RCA section from a 59-year-old white male. This section was taken immediately distal to an occluding thrombus with fragments of thrombus still present in the lumen. A thick, heavy band of T cells extends virtually around the entire circumference (arrows), and this is classified as a Grade IV inflammatory response. H & E stain. Magnification x11.7.

"Active" Inflammatory Atherosclerotic Disease

Active, inflammatory, progressive, expanding atherosclerotic disease is characterized by plaque growth and the development of luminal stenosis, presumably due to continuing and expanding injury produced by the IA. If atherosclerosis is related to arterial wall injury and this injury results in a chronic inflammatory response, then the inflammatory infiltrate associated with an atherosclerotic plaque is a marker of active, injurious atherosclerotic disease [53]. The extent and severity of atherosclerotic lesions, in terms of plaque size, should reflect the extent and severity of arterial wall injury. The severity of this injury, in turn, should be reflected in the extent, magnitude, and/or number of inflammatory cells present, as seen histologically in the artery wall.

Adventitial Inflammation

Table 1 illustrates, in 83 patients who died of acute coronary disease (ACD), the relationship between adventitial inflammatory infiltrates, primarily T lymphocytes, and the extent and severity of atherosclerotic involvement of the epicardial coronary tree, in terms of luminal stenosis. In order to assess the severity and extent of underlying arterial wall injury, adventitial inflammation was estimated and graded on the basis of circumferential involvement by T lymphocytes in the adventitia in each coronary segment. Inflammation or inflammatory cell infiltrates of the intima were not considered in this grading system, but adventitial inflammation was believed to reflect intimal injury [54].

Table 1:. Comparison of luminal stenosis and circumferential extent of adventitial inflammatory involvement of the coronary wall in 83 patients who died of acute coronary disease.

					Severity of Inflammation					
			IC		None		I–II		III–IV	
Degree of Stenosis (%)	# of Sections	%	#	%	#	%	#	%	#	%
<50	3221	46	957	30*	2264	70	899	28	58	2[a]
50–80	2458	35	1623	66	835	34	1453	59	170	7
>80	1377	19	1042	76*	335	24	864	63	178	13[a]
Totals	7056		3622	51	3434	49	3216	45	406	6

IC = Adventitial inflammatory cell involvement; * = p =<0.001; a = p =<0.001

Adventitial inflammation in patients with atherosclerosis is commonly present as discrete foci of T lymphocytes that have congregated at a particular site in the adventitia. They are easily recognized histologically (Figures 5B–5E), and were graded on the basis of I to IV according to the following system: The circumference of each coronary segment was divided into three, 120° quadrants, with the presence or absence of adventitial inflammation in each quadrant recorded. Grade I, the T cells were rather diffusely scattered in the adventitia overlying a plaque without a definite discrete focus (Figures 5A,5B). Grades II, III and IV showed discrete foci in one, two, or all three of the 120° quadrants (Figures 5C–5E). Segments with Grades I, and II inflammation were considered a “mild” injury, whereas Grades III and IV were considered “severe” injury of the artery wall.

In these 83 patients, 3,835 (54%) of over 7000 coronary segments examined histologically showed more than 50% luminal stenosis. These patients had widespread injury and significant plaque development throughout the coronary tree. Similarly, 3,622 (51%) of coronary segments showed adventitial inflammatory infiltrates, confirming the presence of widespread, active, atherosclerotic injury and resulting disease [54].

Seventy-six percent of all coronary segments with >80% luminal stenosis had adventitial inflammation, compared with 30% of coronary segments with <50% luminal stenosis, p=<0.001, proving that the frequency of adventitial inflammation is directly related to plaque size. Comparing the frequency of Grades III/IV adventitial inflammation in the 178 coronary segments with >80% luminal stenosis to the 58 segments with <50% stenosis shows Grades III/IV inflammation is significantly more common in those with >80% stenosis, p=<0.001. Both the frequency and severity of adventitial inflammation, in terms of circumferential extent, are directly related to plaque size [52,55]. We conclude that the size of the plaque and the circumferential extent of adventitial inflammation are directly related to the severity or magnitude of the arterial wall injury.

The Magnitude of Injury

What factors related to the IA determine the magnitude of wall injury? Since plaques vary in size and composition, the amount of IA may not only vary from plaque to plaque but vary in potency, toxicity, virulence, or antigenicity [56]. The susceptibility of the individual patient to the IA must also be taken into account. This variability in the inherent characteristics of the IA could explain why plaques vary in size, in speed of development, and in the degree to which the histologic changes become “advanced” without narrowing the lumen [15]. For example, Figure 2A is a very small plaque with “advanced” changes, including calcification and necrosis, but without adventitial inflammation or stenosis. The IA may be sufficiently potent, or present in sufficient amounts, to cause focal but severe injury. Although the IA may be potent, toxic, or virulent, because this is still a small plaque, the IA is not yet present in sufficie/nt amounts to activate the immune system or present long enough to cause a large plaque to form. In considering the pathogenesis of atherosclerotic injury, we may be dealing not only with the amount, but also the potency, toxicity, virulence, or antigenic potential of the IA.

Luminal Stenosis and Inflammation

Figure 5 illustrates the direct relationship between luminal stenosis and adventitial inflammation. Figures 5A and 5B show a small asymmetric plaque causing approximately 20–30% luminal stenosis along with a Grade I adventitial inflammatory infiltrate, consistent with a small area of focal injury and beginning activation of the immune system. The presence of a necrotic core suggests the presence of an IA sufficiently potent to cause early destruction and necrosis of tissue, similar to, but more advanced than in Figure 2A. Of 23 coronary segments examined from this artery in Figure 5A, 14 showed various degrees of plaque development causing <50% luminal stenosis. Seven of the segments showed Grade I adventitial inflammation, and one segment showed Grade II inflammation. There were no ulcerated plaques (UP) or thrombotic lesions in this artery, nor any coronary calcification. This artery may have been injured in multiple focal areas by a potent IA, actively growing and expanding and beginning to cause activation of the immune system, but not yet causing any plaque ulceration (PU), erosion, or calcification. However, even though the plaque is small and produces no significant luminal stenosis, it is still a vulnerable plaque with a relatively thin fibrous cap. Theoretically it could ulcerate early in plaque development [57]. Figures 5C–5E are examples of Grades III and IV adventitial inflammatory involvement associated with increasing luminal stenosis that illustrate the association between inflammation and luminal stenosis.

Failure of Inflammatory Defenses

The inflammatory defensive responses detailed above appear to be no match for the IA. Specifically, these inflammatory defenses, in spite of what appears to be a vigorous response, fail to neutralize, contain, or remove the IA and/or to halt the spread of the disease at an early stage of plaque development. This observation is similar to those made in regard to the FP response (Chapter 2) in that the FP response also failed to halt the spread of the IA. The failure of these defensive measures suggests the monocytic and/or T lymphocyte responses are either inadequate to deal with the strength or toxicity of the offending agent, or that these inflammatory responses have been altered changed, or subverted in some way from performing their usual protective, reparative functions following wall injury [47]. Leibovich and Ross [36] noted the importance of normally functioning macrophages in wound healing. Therefore, continued plaque growth may reflect either an overwhelming or resistant IA and/or a disabled inflammatory response to injury on the part of macrophages and/or T lymphocytes.

Natural History of Wall Injury

What is the natural history of atherosclerotic wall injury and the associated inflammatory response caused by the IA? Is the IA ever completely neutralized and removed, or can it persist indefinitely in a dormant, inactive state? Table 1 showed 24% of all coronary segments with stenosis greater than 80%

were without adventitial inflammation, similar to the results of other investigators [54]. Some arteries seem able to heal, and the inflammation may subside. This implies that the IA can, in some circumstances, be neutralized, removed, or become dormant, with the injured area undergoing resolution and healing. Plaque growth may be phasic with exacerbations and remissions of the active inflammatory disease process, but the factors causing remission are not known.

Clinical Manifestations of Atherosclerotic Inflammation

One of the great mysteries surrounding active atherosclerosis is the absence of clinical manifestations of inflammation in spite of diffuse inflammatory involvement of the coronary tree (Table 1). Virtually all clinical symptoms of active, progressive atherosclerosis are related to obstruction of coronary blood flow, and to resultant ischemia or infarction of the myocardium. They are not related directly to inflammation. Patients with active atherosclerosis do not exhibit fever, pain, increased sedimentation rate, or a significant increase in white blood count, or other signs of an active inflammatory disease. This suggests that the IA is not exposed to the normal bodily defenses that recognize and remove most IAs. The IA may be residing within a cell and thus escape detection.

In Review

Inflammation, in the form of adventitial T lymphocyte infiltration, follows and responds to atherosclerotic injury and subsequent plaque formation. It is a marker of active, injurious atherosclerotic disease [54,55]. Adventitial inflammation is found only overlying atherosclerotic plaques. It serves to identify the site of injury and, presumably, the location of the IA. The frequency and circumferential extent of adventitial inflammation are directly related to plaque size, and reflect the magnitude of the injury. Plaque growth and the development of luminal stenosis may be due to the continued presence of an active IA that spreads to adjacent tissue, expanding the area of injury and producing increased inflammatory responses. Atherosclerosis and adventitial inflammation are diffuse and widespread in patients who die of ACD. The magnitude of the injury and the speed of plaque development appear to be directly related to the amount, potency, toxicity, or virulence of the IA and/or individual susceptibility to the IA. The inflammatory response to injury fails to halt the growth and spread of the IA. The IA may be too powerful or resistant to these inherent inflammatory defenses, or the macrophage and/or T lymphocyte functions may have been subverted, thereby preventing their neutralizing the IA.

Unanswered Questions

What kind of an IA is this that can apparently alter intracellular mechanisms without killing the cell and can subvert normal defensive responses? What is the mechanism of spread and expansion of the IA? Does the IA replicate and, if so, by what mechanism? Why is the adventitia the site of such heavy infiltration of T lymphocytes compared with the intima, the area of injury? Does the IA, or a byproduct thereof, pass to the adventitia via the lymphatics, with the adventitia functioning much like a regional lymph node? What is the life cycle of the IA and what is the energy source that drives growth and expansion of the plaque?